



National Institute of
Environmental Health Sciences

Powering Research Through Innovative Methods for Mixtures in Epidemiology (PRIME) Program Meeting

Monday, April 29, 2019, 8:30 a.m. – 4:30 p.m.

Tuesday, April 30, 2019, 8:30 a.m. – 2:00 p.m.

NIEHS Building 101, Rodbell Auditorium



https://tools.niehs.nih.gov/conference/prime_2019

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Agenda



Powering Research Through Innovative Methods for Mixtures in Epidemiology (PRIME) Program Meeting

NIEHS Building 101, Rodbell Auditorium – 111 TW Alexander Drive, Research Triangle Park, N.C.

Agenda Monday, April 29, 2019

- 7:15 a.m. Bus Departs From Hotel**
- 8:00 a.m. Registration and Hang Posters** *Lobby*
- 8:30 a.m. Welcome** *Rodbell Auditorium*
Gwen Collman, Ph.D., Director, Division of Extramural Research and Training (DERT),
National Institute of Environmental Health Sciences (NIEHS)
- 8:45 a.m. Background of PRIME and Meeting Goals**
Bonnie Joubert, Ph.D., DERT PRIME Program Director, Population Health Branch, NIEHS
- 9:00 a.m. Commonly-Used Methods for Analyzing Exposure to Mixtures in Environmental Epidemiology:
A Few Examples**
Marianthi-Anna Kioumourtoglou, Ph.D., Columbia University
- 9:30 a.m. Discussion**
- 10:00 a.m. Break**
- 10:15 a.m. Methods for Data Integration and Risk Assessment for Environmental Mixtures**
Chris Gennings, Ph.D., Icahn School of Medicine at Mount Sinai
Brent Coull, Ph.D., Harvard T.H. Chan School of Public Health
- 10:45 a.m. Development and Testing of Response Surface Methods for Investigating the Epidemiology of
Exposure to Mixtures**
Thomas Webster, D.Sc., Boston University
- 11:15 a.m. Estimating the Total Effects of a Mixture of Pollutants on a Health Outcome**
Mary Ellen Turyk, Ph.D., University of Illinois at Chicago
Hua Yun Chen, Ph.D., University of Illinois at Chicago
- 11:45 a.m. Lunch** *NIEHS Cafeteria*
- 1:00 p.m. Bringing Modern Data Science Tools to Bear on Environmental Mixtures**
Marie Lynn Miranda, Ph.D., Rice University
Kathy Ensor, Ph.D., Rice University
- 1:30 p.m. Principal Component Pursuit to Assess Exposure to Environmental Mixtures in Epidemiologic Studies**
Marianthi-Anna Kioumourtoglou, Ph.D., Columbia University
- 2:00 p.m. Structured Nonparametric Methods for Mixtures of Exposures**
David Dunson, Ph.D., Duke University
- 2:30 p.m. Discussion**
Q&A for PRIME PIs and General Discussion
- 3:30 p.m. Poster Session**
- 4:30 p.m. Bus Departs to Hotel**
- 6:00 p.m. Dinner with PRIME PIs**



Powering Research Through Innovative Methods for Mixtures in Epidemiology (PRIME) Program Meeting

NIEHS Building 101, Rodbell Auditorium – 111 TW Alexander Drive, Research Triangle Park, N.C.

Agenda

Tuesday, April 30, 2019

PRIME Grantees and NIEHS Extramural Staff

8:00 a.m. Bus Departs From Hotel

8:15 a.m. Registration

Lobby

9:00 a.m. Closed Discussion
Grantees and NIEHS Extramural Staff

Rodbell AB

Noon Lunch

NIEHS Cafeteria

1:00 p.m. Discussion

2:00 p.m. Bus Departs to Airport





PRIME Grantees' Project Information

Structured Nonparametric for Mixtures of Exposures
David Brian Dunson
Duke University

PROJECT SUMMARY Although it is well known that humans are exposed to a complex mixture of different chemicals, having constituents that change dynamically as an individual ages, very little is known about how these exposures interact to impact health outcomes. The overarching focus in the toxicology and epidemiology literatures has been on examining the health effects of chemicals one at a time. One reason for the lack of consideration of more holistic approaches for simultaneously assessing the health effect of multiple chemicals is the lack of appropriate statistical methods that are interpretable and reliable at disentangling the impact of each chemical in the mixture. When attempts are made to include different chemicals simultaneously in statistical models, most of the focus has been on generic multivariate statistical methods that often fail to have adequate performance. For example, simply including different exposures in nonparametric regression models can lead to unstable estimates due to the so-called curse of dimensionality, particularly if the different exposures are moderately to highly correlated. The overarching goal of this proposal is to develop novel statistical approaches, which are specifically tailored for mixture exposure problems, incorporating mechanistic constraints and supplemental data on chemical structure and toxicological responses to improve performance. An initial focus is on developing restricted nonparametric regression methods, which constrain the response surface to be monotone with possible downturns at low and high doses, consistent with prior data and mechanistic knowledge. Such constraints substantially improve stability and performance in estimating dose response, while facilitating interpretation. Another key advance is the development of mechanistic interaction models, which reduce dimensionality and enable disentangling of main effects and chemical-chemical interactions, allowing no interaction, synergy or antagonism. A further thread designs a novel class of mechanistic response surface models, which directly incorporate supplemental data on chemical structure and borrow information from one-chemical-at-a-time toxicological studies. These models enable de novo prediction of dose response and interactions for new chemicals, which have known structure but have not been studied in toxicology and epidemiology studies. These predictions include an accurate characterization of uncertainty, highlighting cases in which more data are needed. To be appropriate for a rich variety of epidemiological study designs, the methods are generalized to account for covariate adjustments, longitudinal and nested data structures, censoring, and other complications. A key focus of the project is on producing user-friendly software that non-statistician scientists can use to analyze and visualize the health effects of mixture exposures, provided on the project's GitHub site and beta tested. Methods will be tested in a multi-tiered fashion through theoretical studies, comprehensive simulation experiments including comparisons to a rich variety of existing approaches under challenging scenarios, and applications to multiple epidemiology studies. These studies include the MSSM Children's Cohort, NHANES, and CHAMACOS.

**Principle Component Pursuit to Assess Exposure to Environmental Mixtures
in Epidemiologic Studies**

**Marianthi- Anna Kioumourtzoglou
Columbia University Health Sciences**

Project Summary Traditionally, environmental epidemiologic studies have focused on assessing risks related to a single pollutant at a time. This, however, does not reflect reality, since we are constantly exposed to multiple pollutants at once. It is very important, therefore, to be able to assess exposure to pollutant mixtures when conducting environmental epidemiologic methods. Doing so, however, is especially challenging, mainly due to the high dimension of the multi-pollutant exposure matrix (if the exposure of interest includes more than e.g. 5 or 10 chemicals) and because these pollutants are usually very highly correlated with each other. Although some methods are available to address these issues, they usually require strong assumptions and have severe limitations. With this study we propose to bypass most of these limitations by adapting and extending a novel and robust method to assess exposure to multiple pollutants, called Principal Component Pursuit (PCP). We will assess the performance of PCP synthetic datasets representing multiple potential scenarios and study designs and compare our results to those obtained by existing methods. Subsequently, we will apply PCP to three important Public Health issues, i.e. to evaluate the associations between (i) in utero exposure to a mixture of PCBs and neurodevelopment, (ii) exposure to a metals mixture and cardiovascular health, and (iii) exposure to an air pollution mixture and emergency cardiovascular admissions. Finally, we will develop and share software so other researchers can freely use this novel, robust and flexible tool across a plethora of study designs and research questions. Our proposed work will be significant as it will provide epidemiologists with a novel and robust tool to assess exposure to environmental pollutant mixtures.

Bringing Modern Data Science Tools to Bear on Environmental Mixtures
Marie Lynn Miranda
Rice University

Project Summary: Bringing Modern Data Science Tools to Bear on Environmental Mixtures

Environmental exposures often cumulate in particular geographies, and the nature of the complex mixtures that characterize these exposures remains understudied. In addition, adverse environmental exposures often occur in communities facing multiple social stressors such as deteriorating housing, inadequate access to health care, poor schools, high unemployment, crime, and poverty – all of which may compound the effects of environmental exposures. Our central objective is to develop new data architecture, statistical, and machine learning methods to assess how exposure to environmental mixtures shapes educational outcomes in the presence or absence of social stress. We focus on air pollution mixtures, childhood lead exposure, and social stressors. We will implement our proposed work in North Carolina (NC), a state characterized by diverse environmental features, industrial activities, and airsheds typified by varying pollution emission sources and resulting pollutant mixtures. To accomplish this central objective, we will first develop, document, and disseminate methods for building space-time environmental and social data architectures. We will implement this for all of NC, incorporating data on air pollution, lead exposure risk, and social exposures from 1990-2015+ (dataset 1). Second, we will refine methods for linking unrelated datasets to build a space-time child movement and outcome data architecture (dataset 2). Third, we will connect exposures (dataset 1) and outcomes (dataset 2) data via shared geography and temporality into a single, comprehensive geodatabase. Fourth, we will implement increasingly complex methods to assess the effect of environmental mixtures in the presence or absence of social stressors on early childhood educational outcomes. We will document and disseminate all of the underlying methodological work via public website. The proposed work leverages a rich array of data resources already available to the investigators (with some significantly post-processed) and allows tracking of children across space and time. Our team brings tools from modern data science (hierarchical Bayesian methods with variable selection, spatial point process models, machine learning) to bear on the critical question of how environmental mixtures shape child outcomes directly and differentially in the presence of social stress.

Innovative Methodologic Advances for Mixtures in Research in Epidemiology
Mary Ellen Turyk
University of Illinois at Chicago

Abstract Human biomonitoring for chemical exposures has generated large amounts of data. Analysis of those data presents a challenging problem to epidemiologists and biostatisticians. One prominent characteristic of these environmental data is that exposures are always mixtures of chemicals and the chemicals in a mixture are often moderately or highly correlated. The adverse effect of an individual chemical on any health outcome is usually small due to the low exposure level. However, effects of exposure to chemicals in mixtures can accumulate and act synergistically on health outcomes. The overarching goal of this project is to develop better statistical methods for understanding the detrimental health impacts of exposure to mixtures of chemicals. To accomplish this goal, we propose improvements over the existing genome-wide complex trait analysis approach so that the accumulative effects and the total interaction effects of exposure to chemical mixtures can be estimated with minimal bias. We further propose to estimate the individual chemical effects as the average causal effect through the propensity score adjustment. The estimates will serve as the basis for toxicity assessment of chemicals. Lastly, we propose a flexible network analysis approach to understand the potential causal pathways from exposure to mixtures to health outcomes. The methods will be applied to a number of datasets on which the research team has been working to answer important scientific questions with regards to the associations of persistent organic pollutant exposures with endocrine and cardio-metabolic outcomes, and biological pathways and nutrients relevant to these associations. The datasets also serve as testing formats for developing and using the software package implementing the proposed methods. The software package will be made freely available to environmental research community. The results of this project are expected to substantially improve our ability to understand complex relationships among the many chemical exposures found in human populations and detrimental health outcomes. Our development of innovative methods will potentially facilitate the investigation of biological pathways mediating these relationships and enhance our understanding of nutritional and other factors that may in part ameliorate adverse effects of toxicants.

**Development and Testing of Response Surface Methods for Investigating the
Epidemiology of Exposers to Mixtures
Thomas Webster
Boston University**

According to NIEHS, “It is imperative to develop methods to assess the health effects associated with complex exposures in order to minimize their impact on the development of disease.”

NIEHS has held several meetings on mixtures, including the 2015 workshop on Statistical Approaches for Assessing Health Effects of Environmental Chemical Mixtures in Epidemiology Studies. Conclusions include the following. 1) An interdisciplinary perspective is needed, including insights from environmental epidemiology, statistics/mathematics, toxicology and exposure science. 2) Mixtures epidemiology has three key goals: a) identify components of a mixture contributing to the outcome; b) examine interactions between the components; c) construct summary measures of exposure where possible. 3) Different methods have different strengths and weaknesses that may be complementary. We propose to build upon three methods that performed well at the 2015 workshop: Bayesian kernel machine regression (BKMR), exposure space smoothing (ESS) and weighted quantile sum regression (WQS). We will develop two complementary methods: 1) BKMR/ESS. We will expand and combine aspects of BKMR and ESS into one method that primarily addresses the first two goals: variable selection and interactions. Crucial aspects of our proposal are i) extension to binary health outcomes, the most common type of outcome data in epidemiology (the 2015 NIEHS workshop examined continuous outcomes); ii) variable selection using the hierarchical structures observed for correlations between exposures; iii) incorporation of toxicological information. 2) Single index model: We will evaluate a generalization of WQS, the single index model (SIM). SIM non-parametrically estimates a one-dimensional smooth function of a weighted sum of exposures. The weighted sum represents a summary measure of exposure (one based on toxicological principles), a third goal of mixtures epidemiology. Following method development, we will test the methods using both synthetic and real world data sets, including the Environment And Reproductive Health (EARTH) cohort study. We will incorporate causal inference tools such as directed acyclic graphs (DAGs). For example, correlated exposures (co-exposures) are confounders under some DAGs and colliders or intermediate variables under others. This must be taken into account in both generation of synthetic data and proper interpretation of results. The specific aims of this project are as follows:

Specific Aim 1: Combine features of BKMR and ESS to produce a method for analyzing epidemiologic data that incorporates toxicological information; can handle continuous, binary and repeated measures outcome data; select important exposure variables; flexibly model and examine interactions; adjust for confounders; is robust to influential points.

Specific Aim 2: Evaluate the single index model (SIM) as a method for analyzing epidemiologic mixtures data and generating exposure summary measures

Specific Aim 3: Make benchmark synthetic data and method computer code publicly available.

Methods for Data Integration and Risk Assessment for Environmental Mixtures

Chris Gennings

Icahn School of Medicine at Mount Sinai

Brent Andrew Coull

Harvard T.H. Chan School of Public Health,

Project Summary Humans are routinely exposed to mixtures of chemical and other environmental factors, making the quantification of health effects associated with environmental mixtures a critical goal for establishing environmental policy sufficiently protective of human health. Advancing research on mixtures science requires innovation across a span of disciplines in environmental health: exposure science, statistical methods for risk estimation in toxicology and epidemiology, and risk assessment. Accordingly, this proposal structures three specific aims spanning the primary needs in mixtures science: exposure biology (the development of good biomarkers for environmental mixtures), estimation of risk associated with pre- and post-natal exposures to environmental mixtures in children's health, and methods for improving guidance values in risk assessment of mixtures to improve environmental policy. Specifically, incorporating the critical aspect of exposure timing, in Aim 1 we will (1) develop methods that integrate information from studies with highly temporally resolved information on exposure into studies with more temporally targeted biomarker measures; and (2) develop methods that incorporate multiple biomarkers of exposure at varying temporal scales within the same study. Armed with new temporally resolved data on exposure mixtures, in Aim 2, we will develop new classes of models that can assess whether either (1) exposure at one time can “prime” an individual to be more susceptible to a concurrent or subsequent chemical exposure, or (2) exposure to a nutrient or other “protective” exposure at a given time can buffer an individual's tolerance to chemical exposures experienced at other times. However, simply identifying chemicals that are bad actors evidenced through epidemiology data does not adequately inform public health risk assessors about “acceptable ranges” of environmental exposures from consumer products, which is fundamental to regulatory guidelines. In Aim 3, we will develop new classes of models that incorporate and evaluate regulatory guideline values into analyses of health effects of exposure to chemical and nutritional mixtures. Essential to this project is access to motivating data from two on-going pregnancy cohort studies of child development. The PROGRESS study is a cohort in Mexico City. Teeth biomarkers from these children provide a high temporal-resolution record of perinatal exposures to metals. The SELMA study is a large pregnancy cohort in Sweden with prenatal endocrine disrupting chemicals (EDC) exposure and dietary data available, making it possible to test for the potential mitigating effect of good nutrition on health effects from EDCs.



Poster Abstracts

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1. Bayesian Distributed Lag Interaction Models Using Spike and Slab Priors

Joseph Antonelli
University of Florida

Distributed lag models are useful in environmental epidemiology as they allow us to investigate the time periods at which exposure to a pollutant adversely affects health outcomes. Recent studies have focused on estimating the health effects of a large number of environmental exposures on health outcomes. It is important to understand which of these environmental exposures affect a particular outcome, while simultaneously understanding the time periods that are most associated with changes in the outcome. Furthermore, it is possible that these exposures interact with each other such that the effect of one exposure on the outcome depends on the level of other exposures. We propose a Bayesian model to estimate the temporal effects of a large number of exposures on an outcome while allowing for interactions between all the exposures. We use semiparametric functions to estimate the distributed lag curves and employ spike and slab priors to identify the set of important exposures and interactions that affect the outcome. We show the ability of the proposed approach using simulated examples and discuss ongoing work to improve the flexibility and power of the proposed approach.

Coull, B., Harvard T.H. Chan School of Public Health

2. Evaluating the Performance of Generalized Causal Approaches to Risk Assessment: A Simulation Study

Saria S Awadalla

University of Illinois at Chicago

Determination of causal effects is an important analytical step in understanding disease etiology and identifying risk factors. The use of propensity score methods, including weighting, matching, adjusting, covariate balancing, and stratification, have become popular tools in causal inference. These methods, which traditionally pertained to binary exposures, have recently been generalized to accommodate different types of exposures such as categorical or continuous variables. The use of a generalized propensity score (GPS) has had a positive impact in assessing environmental exposures, which are typically measured on the continuous scale and, more importantly, their dose effects are of paramount interest. In this project, we consider various current approaches to using a generalized propensity score and evaluate their applicability in environmental studies. We also introduce a novel GPS-based on order-statistics and contrast its performance to its predecessors. The results of a simulation study, which focuses on evaluating the robustness to deviations from model assumptions and model misspecification of these methods, will be presented.

Rupnow, R.

3. Building a Space-Time Data Architecture Using Disparate Data Sources

Mercedes Bravo
Rice University

Objectives:

Build a space-time environmental and social data architecture for North Carolina, construct a space-time child movement and outcome data architecture, and link these datasets. Data and Methods: We link North Carolina birth records to blood lead level (BLL) screening records and end-of-grade (EOG) standardized test scores in reading and mathematics. The resulting data set is then linked with air pollution and social exposure estimates. The birth, BLL, and EOG data are processed and geocoded to create one record per child, with geocode information at each time point (time of birth, lead screening, and EOG testing). The birth data is the base file to which BLL results and EOG test scores are attached. Linking involves an iterative, deterministic process that allows for fuzzy matching, and only matches that meet a specific threshold are accepted. Neighborhood social factors, specifically racial isolation (RI) and neighborhood deprivation (NDI), are calculated from census data based on a child's residence at birth and EOG testing. Daily ozone (O3) and fine particulate (PM2.5) concentrations from the EPA's Air Quality System and daily Fused Air Quality Surface Using Downscaling (FAQSD) files are used to estimate air pollution exposure in the prenatal period and the period prior to EOG testing, respectively. Air pollution exposures were calculated as prenatal air pollution exposures and pre-EOG exposures. Air pollution exposures at birth are estimated using the nearest air pollution monitor, while air pollution exposures at/prior to EOG testing are estimated based on census tract of residence. NDI and RI are linked to each child based on census tract of residence at birth and at time of EOG testing. Results: Initially, we focus on the cohort of children born in 2000. Using geocoded 2000 births as a base (n=100,395), EOG test results (and geocoding) are added for children successfully linked to the births and for whom both reading and math scores are available (n=65,568). Next, blood lead level information is added to the 2000 births at the individual level (n=52,616). All records at the time of birth are linked to RI/NDI, while 87,174 (87%) have some air pollution exposure estimates. At the time of EOG testing, 54,805 (54.6%) of records are linked to RI, NDI, and air pollution exposure estimates. Conclusion: Future work will focus on extending the linked dataset to include multiple years of linked birth, BLL, and EOG data.

Osgood, C., Rice University
Leong, H., Rice University
Kowal, D., Rice University
Ensor, K., Rice University
Miranda, M.L, Rice University

4. Social Exposures: Racial Isolation and Educational Attainment Isolation

Mercedes Bravo
Rice University

Background. Environmental health researchers require innovative measures of social stressors that can be used to better understand how complex environmental and social exposure mixtures relate to outcomes in children. We previously developed a local, spatial measure of racial isolation (RI) of non-Hispanic blacks (NHB), which measures the extent to which NHB are only exposed to one another. We calculate RI, develop a new measure of educational attainment isolation (EI), and explore the relationship between these two social exposures.

Objectives. Our objectives are to: (1) calculate RI across the study area (NC) at the census tract level; (2) develop and implement a new local, spatial measure of EI across the study area at the census tract level; and (3) assess both global and local measures of correlation between EI and RI to understand how relationships between these metrics vary across space.

Data and Methods. Data used to develop the isolation indices are obtained from 2010 U.S. Census data at the census tract level. Using our previously developed local, spatial measure of RI of NHB, we calculate census tract-level RI by accounting for the population composition in the index tract and adjacent tracts. The index ranges from 0 to 1: with 0 indicating no isolation and 1 indicating complete isolation. We use this method to calculate EI of individuals without a college degree (compared to those with a college degree). In addition to computing a global correlation measure for RI and EI, we calculate a local measure of correlation to evaluate whether the dependency between RI and EI varies across space. **Results.** Tract-level values of RI range from 0.0031 to 0.89, with a mean (median) value of 0.21 (0.17) and a standard deviation of 0.17. Tract-level values of EI range from 0.22 to 0.95, with a mean (median) value of 0.74 (0.78) and a standard deviation of 0.15. The global measure of (Pearson) correlation is 0.23. The local measure of correlation between RI and EI ranges from 0.25 to 0.99, with a mean (median) value of 0.78 (0.83). Clear geographic patterns exist for RI, EI, and the correlation between the two.

Conclusion. These novel measures of the social environment can be developed at multiple geographic scales and at multiple time points. They will serve as input covariates in statistical analyses aimed at understanding the effects of complex mixtures on health and development.

Leong, M.C., Rice University
Ensor, K., Rice University
Miranda, M.L., Rice University

5. Disparities in Air Quality Modeling Uncertainty Across Social and Demographic Indicators in North Carolina

Alexander Bui
Rice University

Socioeconomically disadvantaged populations are commonly exposed to higher concentrations of air pollution. However, there is limited research on the relationship between demographics and uncertainties in air quality predictions. Using predictions of PM_{2.5} and O₃ in North Carolina (NC) from the Bayesian space-time downscaling fusion model (downscaler) from 2010 at the census tract level, this study investigates the spatial relationships between demographic data and downscaler modeling uncertainty. The downscaler model uses both numerical modeling output and monitoring data to predict concentrations at new spatial scales. Downscaler model uncertainties, derived from the standard deviations of “posterior” distributions estimated for each space-time point, include the uncertainty of the predicted 24-hour averaged PM_{2.5} concentrations and daily maximum eight-hour O₃ concentrations. Demographic data include race, age, household income, poverty level, and neighborhood quality, among other factors. Generally, the downscaler model uncertainty associated with each concentration prediction is small relative to the predicted concentrations (~20–40%); it is typically smaller in regions with more densely situated monitors (urban areas) and larger in regions with more sparse monitoring networks (rural areas). This trend holds true for the continental U.S. (lower uncertainty in the eastern U.S. and higher uncertainty in the western/Midwestern U.S.), as well as in NC. However, it has yet to be determined how census tract geography and demographics with low downscaler model uncertainty compare to those with high downscaler model uncertainty. Therefore, in addition to quantifying how concentrations of PM_{2.5} and O₃ change across NC over space and time, this study aims to identify and understand geographical disparities between the upper and lower quintiles of modeling uncertainty for PM_{2.5} and O₃. Furthermore, this study will investigate socioeconomic disparities between population groups between the upper and lower quintiles of modeling uncertainty for PM_{2.5} and O₃. Ultimately, this analysis is important for policymakers and researchers as it will aid in the assessment of uncertainty of air quality predictions used in exposure estimations and the impact on the associated communities, especially in those associated with high modeling uncertainty.

Griffin, R., Rice University
Osgood, C., Rice University/CEHI
Tootoo, J., Rice University/CEHI
Bravo, M., Rice University/CEHI
Ensor, K., Rice University
Miranda, M., Rice University/CEHI

6. Latent Classes for Meaningful Chemical Mixtures Analyses in Epidemiology: An Example Using Phthalate and Phenol Exposure Biomarkers in Pregnant Women

Rachel Carroll
University of North Carolina at Wilmington

Latent class analysis (LCA), although minimally applied to the statistical analysis of mixtures, may serve as a useful tool for identifying individuals with shared real-life profiles of chemical exposures. Knowledge of these groupings and their risk of adverse outcomes has the potential to inform targeted public health prevention strategies. This example applied LCA to identify clusters of pregnant women within the LIFECODES birth cohort with shared exposure patterns across a panel of urinary phthalate metabolites and parabens, and to evaluate the association between cluster membership and urinary oxidative stress biomarkers. The latent classes identified individuals with: “low exposure,” “low phthalates, high parabens,” “high phthalates, low parabens,” and “high exposure.” Class membership was associated with several demographic characteristics. Compared to “low exposure,” women classified as having “high exposure” had elevated urinary concentrations of the oxidative stress biomarkers 8-hydroxydeoxyguanosine (19% higher, 95% confidence interval [CI]=7%, 32%) and 8-isoprostane (31% higher, 95% CI=-5%, 64%) 25% higher, 95% CI=0%, 57%). However, contrast examinations indicated that associations between oxidative stress biomarkers and “high exposure” were not statistically different from those with “high phthalates, low parabens,” suggesting a minimal effect of higher paraben exposure in the presence of high phthalates. The presented example offers verification through application to an additional data set as well as a comparison to another unsupervised clustering approach, k-means clustering. LCA may be more easily implemented, more consistent, and more able to provide interpretable output.

White, A.J.
Keil, A.P.
Meeker, J.D.
McElrath, T.F.
Zhao, S.
Ferguson, K.K.

7. Estimating Associations of Metal Mixtures with Adolescent Cognition in the Presence of Missing Data: Use of Bayesian Kernel Machine Regression with Multiple Imputation

Birgit Claus Henn
Boston University

Although chemical mixtures research is increasingly popular, data on effects of metal mixtures on adolescent health remain sparse. We estimated associations of a metal mixture with general cognitive ability in adolescents residing near ferromanganese industry, a source of airborne metals emissions. We measured manganese (Mn), lead (Pb), copper (Cu), and chromium (Cr) in hair, blood, urine, nails, and saliva collected from 635 Italian adolescent participants of the PHIME (Public Health Impact of Metals Exposure) Study. Full-scale, verbal, and performance IQ (FSIQ, VIQ, PIQ) scores were measured using the Wechsler Intelligence Scale for Children (WISC-III). As is common in epidemiologic studies, data were missing on several key variables. We therefore employed multiple imputation to impute missing values using chained equations. We applied Bayesian kernel machine regression (BKMR) to estimate associations of IQ with the metal mixture in each imputed dataset and then combined information across imputations. In secondary analyses, we used BKMR's hierarchical variable selection option to inform the choice of biomarker for Mn, Cu, and Cr. Adjusting for potential confounders, we observed an inverted u-shaped association between hair Cu and VIQ, consistent with Cu as an essential nutrient that is neurotoxic in excess. When Cu was set at its 10th percentile, the joint increase of Mn, Pb, and Cr from their respective 50th to 75th percentiles was associated with a 1.4 (95% CI: -2.6, -0.2) point decrease in VIQ score. There was suggestive evidence of interactions between Mn and Cu. In secondary analyses, biomarkers associated most strongly with VIQ score were saliva Mn, hair Cu, and saliva Cr. Our work supports further investigation into the nonlinearity of Cu and the joint and interactive associations of Mn, Cu, and Pb with neurobehavior. This analysis demonstrates the application of BKMR across multiple imputed datasets to address a common epidemiologic scenario of missing data, as well as an innovative use of the hierarchical variable selection procedure in BKMR.

Bauer, J.A., Boston University
Devick, K., Harvard Chan School of Public Health
Bobb, J.F., Kaiser Permanente Washington Health Research Institute
Placidi, D., University of Brescia, Italy
Oppini, M., University of Brescia, Italy
Wright, R.O., Icahn School of Medicine at Mount Sinai
Smith, D.R., University of California, Santa Cruz
Lucchini, R.G., Icahn School of Medicine at Mount Sinai
Webster, T.F., Boston University
Coull, B.A., Harvard Chan School of Public Health

8. Bayesian Kernel Machine Causal Mediation Analysis

Katrina Devick

Harvard T.H. Chan School of Public Health

It is important to understand the mechanisms through which a mixture operates in order to reduce the burden of disease. Currently, there are few methods in the causal mediation analysis literature to estimate the direct and indirect effects of an exposure mixture on an outcome operating through an intermediate (mediator) variable. We present new statistical methodology to estimate the natural direct effect (NDE), natural indirect effect (NIE), and controlled direct effects (CDEs) of a potentially complex mixture exposure on an outcome through a mediator variable. We implement Bayesian kernel machine regression (BKMR) to allow for all possible interactions and nonlinear effects of the co-exposures on the mediator, and the co-exposures and mediator on the outcome. From the posterior predictive distributions of the mediator and the outcome, we simulate counterfactual outcomes to obtain posterior samples, estimates, and credible intervals (CI) of the NDE, NIE, and CDE. We perform a simulation study that shows when the exposure-mediator and exposure-mediator-outcome relationships are complex, our proposed Bayesian kernel machine regression – causal mediation analysis (BKMR-CMA) preforms better than current mediation methods. We apply our methodology to quantify the contribution of birth length as a mediator between in utero coexposure of arsenic, manganese, and lead, and children’s neurodevelopment, in a prospective birth cohort in rural Bangladesh. We found a negative association of coexposure to lead, arsenic, and manganese and neurodevelopment, a negative association of exposure to this metal mixture and birth length, and evidence that birth length mediates the effect of coexposure to lead, arsenic, and manganese on children’s neurodevelopment. If birth length were fixed to its 75th percentile value of 48 cm, the effect of the metal mixture on neurodevelopment decreases, suggesting that nutritional interventions to help increase birth length could potentially block some of the harmful effects of the metal mixture on neurodevelopment.

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9. Bayesian Factor Analysis for Inference on Interactions

Federico Ferrari
Duke University

This article is motivated by the problem of estimating interactions among chemical exposures on human health outcomes. Chemicals often co-occur in the environment or in synthetic mixtures and as a result exposure levels can be highly correlated. For these reasons, interaction effects between chemicals need to be considered in order to study their impact on human health. We propose a novel method that exploits the correlation structure of the predictors and allows us to estimate interaction effects in high dimensional settings. We propose a latent factor joint model, which includes shared factors in both the predictor and response components while assuming conditional independence. By including a quadratic regression in the latent variables in the response component, we induce flexible dimension reduction in characterizing main effects and interactions. We propose a Bayesian approach to inference and show the computational advantages of Factor analysis for INteractions (FIN). FIN can be generalized to higher order interactions, allowing increasing shrinkage as the order of interactions increases. We also propose an extension to allow multivariate outcomes using Structural Equation Model. We provide theory on posterior consistency and the impact of misspecifying the number of factors. We evaluate the performance using a simulation study and data from the Collaborative Perinatal Project. Code is available on GitHub.

Dunson, D., Duke University

10. Identifying Main Effects and Interactions Among Exposures Using Gaussian Processes

Federico Ferrari
Duke University

This article is motivated by the problem of studying the joint effect of different chemical exposures on human health outcomes. This is essentially a nonparametric regression problem, with interest being focused not on a black box for prediction but instead on selection of main effects and interactions. For interpretability, we decompose the expected health outcome into a linear main effect, pairwise interactions, and a non-linear deviation. Our interest is in model selection for these different components, accounting for uncertainty and addressing non-identifiability between the linear and nonparametric components of the semiparametric model. We propose a Bayesian approach to inference, placing variable selection priors on the different components, and developing a Markov chain Monte Carlo (MCMC) algorithm. A key component of our approach is the incorporation of a heredity constraint to only include interactions in the presence of main effects, effectively reducing dimensionality of the model search. We adapt a projection approach developed in the spatial statistics literature to enforce identifiability in modeling the nonparametric component using a Gaussian process. We also employ a dimension reduction strategy to sample the non-linear random effects that aids the mixing of the MCMC algorithm. The proposed MixSelect framework is evaluated using a simulation study and is illustrated using data examples. Code is available on GitHub.

Dunson, D., Duke University

11. Per- and Polyfluoroalkyl Substances and Bone Mineral Density in Mid-Childhood

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Background: Identifying factors that impair bone accrual is a critical step toward osteoporosis prevention. Exposure to per- and polyfluoroalkyl substances (PFASs) has been associated with lower bone mineral density, but data are limited, particularly in children. **Methods:** We studied 576 children in Project Viva, a Boston-area cohort of mother/child pairs recruited prenatally 1999-2002. We quantified plasma concentrations of several PFASs and measured areal bone mineral density (aBMD) by dual-energy X-ray absorptiometry in mid-childhood. We used single PFAS linear regression models to examine associations between plasma concentrations of each PFAS with aBMD Z-score. We used weighted quantile sum regression to examine the association of the PFAS mixture with aBMD Z-score, accounting for collinearity between PFASs. All models were adjusted for maternal age, education, annual household income, census tract median household income, and child age, sex, race/ethnicity, dairy intake, physical activity, and year of blood draw. **Results:** Children were (mean \pm SD) 7.9 ± 0.8 years of age. Plasma PFAS concentrations were highest for perfluorooctane sulfonate (PFOS) (median [IQR] 6.4 [5.6] ng/mL) and perfluorooctanoate (PFOA) (median [IQR] 4.4 [3.2] ng/mL). Using linear regression, children with higher plasma concentrations of PFOA, PFOS, and perfluorodecanoate (PFDA) had lower aBMD Z-scores (e.g., beta: -0.16 ; 95% CI: -0.25 , -0.06 per doubling of PFOA). The PFAS mixture, driven by PFDA, 2-(N-methyl-perfluorooctane sulfonamide) acetate (MeFOSAA), PFOA, and PFOS, was negatively associated with aBMD Z-score (beta: -0.16 ; 95% CI: -0.28 , -0.04 per IQR increment of the mixture index). **Conclusions:** Higher exposures to both individual PFASs and the PFAS mixture were associated with lower aBMD in childhood. PFAS exposure may impair bone accrual in childhood and peak bone mass, an important determinant of lifelong skeletal health.

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12. Overview of Commonly-Used Methods to Analyze Exposure to Mixtures in Environmental Epidemiology

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Numerous methods have been developed or adapted from other fields to allow environmental epidemiologists to assess exposure to mixtures in health studies. Current and future methods should be employed with a specific research question in mind; as different methods exist to answer different questions, results from analyses using different methods are expected to vary. We thus emphasize the importance of choosing the appropriate mixtures method to answer a specific a priori defined research question(s), as the results of different methods are interpreted quite differently. Here, we present and discuss some examples of existing mixtures methods that can be employed to address distinct research questions. Specifically, we discuss these main research questions: (1) Are there specific exposure patterns in the study population? (2) Which are the toxic agents in the mixture? (3) Are mixture members acting synergistically? (4) If some prior knowledge — or a predefined hypothesis — exists about how the different mixture members may group, what are the group-specific effects? (5) What is the overall effect of the mixture? Some of the methods discussed, but not all, also allow for non-linear exposure-response relationships, and some methods can be used to address more than one research question. Although to-date, and to the best of our knowledge, no single method exists to answer all mixtures questions, with a well-defined research question and advanced mixture methods, researchers are better equipped to explore the complex relationships between environmental mixtures and adverse health outcomes.

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13. Patterns of Phenol, Paraben, and Phthalate Exposure in New York City Women

Elizabeth A. Gibson

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Background. Women are disproportionately exposed to environmental chemicals linked to adverse health outcomes through their use of personal care products. Identification of exposure patterns and associations with potential exposure sources can inform the design of targeted policies and interventions. **Methods.** We used information on pregnant women aged 18–35 from New York enrolled in the Mothers and Newborns cohort. Five phenols, three parabens, and nine phthalate metabolites were measured and adjusted for specific gravity in spot urine samples collected during the third trimester in 362 women. Personal care product use was assessed via questionnaire. We used principal component pursuit (PCP), a novel robust pattern recognition and dimensionality reduction technique, to simultaneously identify consistent patterns of chemical exposure and to isolate unique or extreme exposure events. We included individual pattern scores in regression models to evaluate their relationship with personal care product use. **Results.** Separating variance due to extreme events from common patterns, PCP explained 81% of the variance in exposure. We identified five patterns that 1) represent overall exposure, 2) separate phthalates from phenols and parabens, 3) separate two phenols (2,4-dichloro-phenol and 2,5-dichloro-phenol) from parabens, 4) separate di(2-ethylhexyl) phthalate metabolites from other phthalates, and 5) represent disproportionately high triclosan exposure. Personal care products contain varying mixtures of these chemicals. Pattern 1 was associated with make-up, perfume, and liquid soap use. Pattern 2 was associated with eye make-up and hair gel use. Pattern 3 was associated with lotion use. Pattern 4 was associated with lotion, hair spray, and sunscreen use. Pattern 5 was associated with lipstick and deodorant use. **Conclusions.** Phenol, paraben, and phthalate exposure comes from various environmental sources, including personal care products. PCP serves as a useful tool to aggregate exposures into consistent patterns that, if found to be related to adverse health, are amenable to targeted public health messaging.

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14. SEEM: Selecting Key Environmental Exposures in Mixtures

Jiyeong Jang

In understanding the role of mixtures of exposures on cardiometabolic outcomes, the question of statistical selection of important exposures can be challenging since the number of environmental exposures are often large, strongly inter-correlated among themselves, and many may have weak individual effects on the outcome. Statistical variable selection has become an essential element of environmental modeling to yield parsimonious models while keeping high prediction accuracy. In our investigations with data sets considered in this PRIME project, we, in particular, find that the levels of mixture environmental exposures are strongly collinear, and, at the same time, the individual effect of each is weak on the cardiometabolic outcome. Regularized variable selection methods such as Least Absolute Shrinkage and Selection Operator (LASSO) have become popular for statistical variable selection. We, however, find that these methods may fail to select any of the exposures in the mixture even though many of the them have significant marginal (univariable) association with the outcome. We are developing a method for Selection of key Environmental Exposures in Mixtures (SEEM) which we project will provide improved prediction accuracy by efficiently handling the collinearity problem through iterative procedures of selecting exposures after clustering highly correlated exposures. The performance of this method is evaluated in an extensive set of simulation studies.

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15. A Tool for Estimating Lead Exposure Risk at Fine Spatial Scales

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Rice University

Environmental and social exposures may affect cognitive outcomes and academic achievement. Lead has been well-documented as a neurotoxicant and linked to a variety of adverse cognitive and educational outcomes. However, we do not have blood lead screening data on all children in our PRIME study area. Thus, developing a broadly available assessment of childhood lead exposure risk will substantially increase our ability to jointly assess the impact of social and environmental stressors on educational outcomes. The Children's Environmental Health Initiative has developed a childhood lead exposure risk model that combines county tax assessor, blood lead screening, and U.S. Census data to create individual tax parcel level relative assessments of likely exposure to biologically available lead. The model has previously been validated by field collection of environmental samples. We have expanded the model to all North Carolina counties that provide the requisite tax parcel data. We combine county tax assessor information with georeferenced NC blood lead testing results and U.S. Census data via shared geography. We fit our model using geocoded blood lead surveillance records from 1992 to 2015 for all NC counties with the required tax assessor information (n=50 of 100). Log-normalized blood lead levels served as the dependent variable, with five explanatory variables along with a county indicator. We then apply the vector of coefficients resulting from the regression model to every tax parcel in the 50 counties. We estimate the relative risk of exposure to biologically available lead across 1,454,921 residential tax parcels. Percentage African American, percentage Hispanic, and percentage receiving public assistance are positively and significantly associated with blood exposure risk; year of construction and median household income are negatively and significantly associated with blood lead level. Statewide, we observe patterns of higher risk for lead exposure in lower income, minority communities with aged housing stock. These results are consistent with our previously published model estimates for six NC counties. We use the model as a means to calculate the relative risk for childhood lead exposure for the 1,006,711 (69%) parcels lacking blood lead screening data. This information gain will be incorporated into our larger evaluation of the joint effects of social and environmental exposures on educational outcomes.

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16. Modeling Complex Associations Among Social and Environmental Mixtures and Educational Outcomes

Man Chong Leong
Rice University

Environmental (e.g., air pollution, lead) and social exposures (e.g., deprivation, segregation) may affect cognitive outcomes and academic achievement. However, little is known about the interactions among environmental exposures and social conditions, and associations with educational outcomes remain unclear. The objectives of this study are to: (1) identify environmental and social exposures that are associated with educational outcomes; (2) develop methods for incorporating complex mixtures in assessing the impact of environmental and social exposures, both separately and in combination, on educational outcomes; and (3) consider environmental and social exposures (and interactions) that occur at different time points along the life course, including birth and childhood. We link statewide, geocoded North Carolina birth data (2000) to blood lead surveillance records (2000 - 2011) and educational outcome data, specifically end-of-grade (EOG) standardized test scores in reading and mathematics in fourth grade (2010-2011). This longitudinal dataset is then linked with census tract level measures of air pollution, including fine particulate matter (PM_{2.5}) and ozone (O₃) concentrations; the Neighborhood Deprivation Index (NDI); and Racial Isolation (RI). The resulting analysis data set included n=17,436 children. Variable selection and regression analyses are performed on EOG reading scores. We apply three methods for variable selection: LASSO, Elastic Net, and Bayesian Joint Variable Selection. Bayesian additive regression trees and generalized additive models are used to estimate nonlinear associations between environmental and social exposures and EOG reading scores, as well as interactions. Out of 51 main effect variables, 26 were selected; of 28 interaction effects, five were selected. For main effects, air pollution in the early prenatal period (1st trimester), birthweight percentile for gestational age, blood lead level, maternal race/ethnicity, having a learning disability, and neighborhood RI and NDI were associated with EOG reading scores. Significant interactions were observed for: (1) NDI and acute air exposures (estimated PM_{2.5} and O₃ exposure for the 30 days prior to the test date); (2) RI and longer-term PM_{2.5} exposure (estimated for the year prior to the test date); and (3) blood lead levels and RI at birth. Environmental exposures, blood lead level, RI and NDI are associated with academic achievement both individually and interactively.

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Ensor, K.
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17. A Robust Hypothesis Test for Continuous Nonlinear Interactions in Nutrition-Environment Studies: A Cross-validated Ensemble Approach

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Harvard University

Gene-environment and nutrition-environment studies often involve testing of high-dimensional interactions between two sets of variables, each having potentially complex nonlinear main effects on an outcome. Construction of a valid and powerful hypothesis test for such an interaction is challenging, due to the difficulty in constructing an efficient and unbiased estimator for the main effects of potentially complex form. In this work we address this problem by proposing a Cross-validated Ensemble of Kernels (CVEK) that learns the space of appropriate functions for the main effects using a cross-validated ensemble approach. With a carefully chosen library of base kernels, CVEK estimates the form of the main-effect functions from the data, and guards against over-fitting under the alternative. The method is motivated by a study on the interaction between metal exposures in utero and maternal nutrition on children's neurodevelopment in rural Bangladesh. The proposed tests identified evidence of an interaction between minerals and vitamins and arsenic and manganese exposures and was more powerful than existing approaches. Results suggest that the detrimental effects of these metals are most pronounced at low levels of the nutrients, suggesting nutritional interventions in pregnant women could mitigate the adverse impacts of in utero metal exposures on children's neurodevelopment.

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Valeri, L.
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18. Bayesian Joint Modeling of Chemical Structure and Dose Response Curves

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When the Toxic Substances Control Act was enacted in 1976, roughly 60,000 existing chemicals were considered safe for use and grandfathered in. Today there are approximately 85,000 chemicals on the list, with around 2,000 new chemicals introduced each year. It is impossible to screen all of these chemicals via full-organism in vivo studies. High-throughput toxicity screening (HTS) programs allow for the relatively cheap and fast collection of dose-response information in vitro, which can provide clues as to chemicals' potential toxic effects. We propose to use these HTS dose-response curves as supervision information of a sparse linear dimension reduction of structural features. Specifically, we propose a Bayesian partially shared latent factor joint model imposing sparsity on chemical structure loadings and smoothness on dose-response loadings. This framework makes it possible to learn which chemical structural elements are related to toxicological activity, and how linear combinations of features impact a chemical's dose response. Additionally, this model can be used to generate a coherent pairwise distance metric informed by both chemical structure and toxicity. Chemicals close in feature-response distance could be assumed to have similar effects. Thus, such a distance metric could be used when assessing new chemicals for which no dose-response information is yet available. It could also be used to inform the main effects in a mixture model. We show preliminary performance results compared to existing methods.

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19. An Overview of Methods to Address Distinct Research Questions on Environmental Mixtures: An Application to Persistent Organic Pollutants and Leukocyte Telomere Length

Yanelli Nunez
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Background. Multiple methods exist to analyze environmental mixtures in health studies. To illustrate the differences among methods based on the research question each answer, we employed methods geared toward distinct research questions in a sample concerning persistent organic pollutants (POPs) as a mixture and leukocyte telomere length (LTL) as an outcome. **Methods.** With information on 18 POPs and LTL among 1,003 U.S. adults (NHANES, 2001-2002), we used unsupervised methods including clustering to identify profiles of similarly exposed participants, and Principle Component Analysis (PCA) and Exploratory Factor Analysis (EFA) to identify common exposure patterns. We also applied supervised learning techniques including penalized, weighted quantile sum (WQS), and Bayesian kernel machine (BKMR) regressions to identify potentially toxic agents and characterize nonlinear associations, interactions, and the overall mixture effect. **Results.** Clustering separated participants into high, medium, and low POP exposure groups; longer log-LTL was found among those with high exposure. The first PCA component represented overall POP exposure and was positively associated with log-LTL. Two EFA factors, one representing furans and the other PCBs 126 and 118, were positively associated with log-LTL. Penalized regression methods selected three congeners in common (PCB 126, PCB 118, and furan 2,3,4,7,8-PNCDF) as potentially toxic agents. WQS found a positive overall effect of the POP mixture and identified six POPs as potentially toxic agents (furans 1,2,3,4,6,7,8-HXCDF; 2,3,4,7,8-PNCDF; and 1,2,3,6,7,8-HXCDF; and PCBs 99, 126, 169). BKMR found a positive linear association with furan 2,3,4,7,8-PNCDF, suggestive evidence of linear associations with PCBs 126 and 169, and a positive overall effect of the mixture, but no interactions among congeners. **Discussion.** Using different methods, we identified patterns of POP exposure, potentially toxic agents, the absence of interaction, and estimated the overall mixture effect. These applications and results may serve as a guide for mixture method selection based on specific research questions.

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20. Modeling of Dependence in High-Dimensional Data: Bayesian Latent Factor Modeling in R

Evan Poworoznek
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Statistical modeling problems involving groups of highly correlated sets of variables are commonplace. Chemical mixtures data are a clear case of this class of problems, involving observations of many metabolites corresponding to different chemical exposures. Factor modeling is a flexible method for identifying groups of related covariates and performing analysis with these grouped factors. Recent work has introduced general new Bayesian methodologies for performing factor modeling on large-scale data. We introduce a package in the R programming environment for easy implementation of these factor modeling methods both for a fixed number of factors, and in the presence of uncertainty in the number of factors. We provide flexible functions for covariance matrix factorization, estimation of latent factors, and latent factor regression for relating correlated predictors to outcome variables, including in the presence of interactions. We provide fast and efficient post-processing functions to enforce identifiability on samples of the factor loadings matrix. We facilitate meta-analysis of shared factors in multiple studies within a Bayesian hierarchical framework. Source code for all functions is available on GitHub:

https://github.com/poworoznek/sparse_bayesian_infinite_factor_models

Dunson, D., Duke University

21. A Novel Risk Assessment Model for Incorporating Co-exposures Provides Preliminary Guideline Values for Unregulated Chemicals

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INTRODUCTION: Traditional risk assessment provides guideline values based on single chemical evaluations, primarily using animal models. However, results do not account for multiple chemical exposures, may not adequately reflect human dose-response, and guideline values for internal concentrations are unavailable for many chemicals commonly detected in human biomonitoring. The Acceptable Concentration Range (ACR) model, a novel nonlinear dose-response model that incorporates co-exposures, previously found points of departure (POD) for 11 compounds below published Human Biomonitoring (HBM) or Biological Equivalent (BE) values when applied to epidemiologic data. Here, we extend the ACR model to provide PODs for 15 additional chemicals. **METHODS:** We applied the ACR model to 26 prenatally measured compounds ($\mu\text{g/L}$) in relation to birthweight among the population-based Swedish Environmental Longitudinal, Mother and child, Asthma and allergy (SELMA) pregnancy cohort of 1,357 mother-child pairs to (1) estimate mean PODs from 100 bootstrap samples; (2) assess how the ACR model scaled when analyzed for single compounds, chemical class groups, or a full mixture; and (3) estimate the mean mixture uncertainty factor (MAF) for regulated chemicals. **RESULTS:** Consistent with prior analyses of 11 compounds, PODs were below published HBM/BE values for many chemicals (e.g., MEP POD = 809 vs. HBM = 18,000 $\mu\text{g/L}$). Where guideline values were unavailable, up to 58% of the study population had biomarker levels above estimated chemical class PODs (e.g., 3-phenoxy-benzoic acid). PODs derived from the chemical class models were lower than single chemical models (mean = 36% lower). Full mixture PODs varied widely, reflecting model uncertainty. Mean MAFs ranged from 1.8 to 6.9. **CONCLUSION:** When accounting for co-exposures in a sensitive human population, our results indicate that current regulatory guidelines may be too high. Where guideline values are unavailable, estimated PODs suggest that exposure to unregulated compounds may be impacting a substantial portion of the general population. The ACR model may provide empirical estimates for determining MAFs for single chemical guideline values. Future research will evaluate ACR model performance under varying assumptions and estimated POD generalizability to other study populations.

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22. Estimation of Weak Effects of a Mixture of Pollutants on a Health Outcome

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Environmental pollutants are usually composed of mixtures of many chemicals that are highly correlated due to similar sources, chemical structures, and chemical properties such as lipophilicity. Because of the usual low dosage levels of exposures to environmental pollutants, the effect of an individual chemical on a health outcome is often weak and difficult to detect. In addition, the health effects of the exposure to pollutants can be substantially heterogeneous despite of the structural similarity of the pollutants. All of these features make the detection of health effects of mixtures of pollutants very challenging by traditional statistical analysis approaches. We proposed a new approach to estimating the overall effects of a mixture of pollutants by extending the method for estimating phenotype variation attributable to the single nucleotide polymorphisms, namely, the narrow-sense heritability. Our extension overcomes the possible bias induced by the high correlation among the chemicals when the original method is used. The extension also enables us to estimate the total main and interaction effects among the mixture of pollutants on a health outcome. Extensive simulation studies suggest the proposed approach can estimate the total variation of the health outcome explained by the pollutants mostly unbiasedly. We applied the proposed approach to the estimation of the total effects of PCBs on the standardized glycohemoglobin level in a subset of the NHANES data and find that about 5–10% of the standardized glycohemoglobin variation is associated with the PCBs.

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23. Blood BTEX Levels and Neurologic Symptoms in Gulf States Residents

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Background: The chemicals benzene, toluene, ethylbenzene, and xylenes (BTEX) are neuroactive. Exposures often co-occur because they share common sources, including cigarette smoke, automobile exhaust, and industrial emissions. We examined neurologic effects of environmental BTEX exposure among U.S. Gulf Coast residents taking into account concomitant exposures. **Methods:** We measured blood concentrations of BTEX in 690 Gulf state residents. Blood BTEX were analyzed using equilibrium headspace solid-phase micro-extraction with benchtop gas chromatography/mass spectrometry using standard procedures at the Centers for Disease Control and Prevention National Center for Environmental Health. Neurologic symptoms were ascertained via telephone interview. We used log-binomial regression to estimate associations (PR, prevalence ratio) between blood BTEX levels and self-reported neurologic symptoms independently for the presence of any neurologic, central (CNS), or peripheral nervous system (PNS) symptoms. We estimated associations in single chemical models mutually adjusted for co-occurring BTEX and used weighted quantile sum regression to model associations (OR, odds ratio) between the combined BTEX mixture and neurologic symptoms. **Results:** Half (49%) of participants reported at least one neurologic symptom. Each BTEX chemical was associated with increased CNS and PNS symptoms in single-chemical models comparing the highest to lowest quartile of exposure. After adjusting for coexposures, benzene was associated with CNS symptoms among all participants (highest vs lowest quartile, PR=2.13, 95% CI: 1.27, 3.57; p-trend=0.01) and among nonsmokers (highest vs lowest quartile, PR=2.30, 95% CI: 1.35, 3.91; p-trend=0.01). Coexposure-adjusted associations with toluene were apparent for reporting multiple PNS symptoms among all participants (highest vs lowest quartile, PR=2.00, 95% CI: 0.96, 4.16; p-trend=0.04) and nonsmokers (highest vs lowest quartile, PR=3.11, 95% CI: 1.13, 8.52; p-trend=0.02). In mixture analyses, a one-quartile increase in BTEX exposure was associated with neurologic symptoms (OR=1.47, 95% CI: 1.11, 1.98). The weighted quantile sum index weighted benzene most heavily, which was consistent with single chemical analyses. **Conclusions:** Increasing blood benzene concentration was associated with increased prevalence of CNS symptoms in single-chemical and mixture analyses. In this sample, BTEX-associated neurologic effects are likely driven by exposure to benzene and, to a lesser extent, toluene.

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24. Kernel Machine and Distributed Lag Models for Assessing Critical Windows to Mixtures of Time-Varying Environmental Exposures in Children's Health Studies

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Research has shown that early life exposures to environmental chemicals, starting as early as conception, can reprogram the developmental process and result in altered health status later in life. We consider statistical methods to estimate the association between mixtures of multiple time-varying exposures and a future health outcome, e.g., exposure to multiple air pollutants observed weekly throughout pregnancy and birth weight. First, we illustrate how to use traditional distributed lag models, distributed lag nonlinear models, and Bayesian kernel machine regression to estimate the association between multiple time-varying exposures and a health outcome. While none of these methods simultaneously account for exposure-timing, nonlinear association, and interactions, we highlight situations in which each model performs well. Second, we propose a new method to estimate the association between multiple time-varying exposures and a health outcome. The proposed approach is, to our knowledge, the first method to simultaneously account for exposure-timing, nonlinear associations, and interactions between time-varying exposures. The proposed approach is a Bayesian kernel machine regression method that accounts for exposure timing using a functional weight component within the kernel. The weight function identifies developmental periods with increased association between exposure and a future health outcome, often referred to as a critical window of exposure. We demonstrate the proposed methods in an analysis of exposure to four ambient pollutants and birth weight in a Boston-area perinatal cohort.

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Biographies

Toccara Chamberlain

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Toccara Chamberlain is a health specialist with the NIEHS Population Health Branch in the Division of Extramural Research. She provides analytical support for many of the branch's activities including the Research to Action program and the Powering Research Through Innovative Methods for Mixtures in Epidemiology (PRIME) program. Toccara received her master's degree in mental health counseling from Webster University and her bachelor's degree in sociology from UNC Greensboro. She started her career with the NIH as a Presidential Management Fellow in 2013 and has had experience with multiple Institutes and Centers. Prior to joining the NIH, Toccara was a member of the United States Army Reserves where she served as a mechanic and automated logistical specialist for almost 12 years.

Hua Yun Chen

The University of Illinois at Chicago

Hua Yun Chen, Ph.D., is a professor of biostatistics at the division of epidemiology and biostatistics at the University of Illinois at Chicago School of Public Health. His primary area of research involves developing statistical methods for handling incompletely observed data in statistical analysis. Incompletely observed data includes data with missing values and censored data. Chen's second area of methodology development is analyzing biased sampling designs, including the conventional case-control and matched case-control designs, and the more complex sampling designs such as the extreme-values sampling design, two-stage sampling designs, and case-cohort sampling designs. In addition, he has also developed semiparametric odds ratio models for studying gene-environmental interactions and high-dimensional networks. The methods he has developed have been applied to studies of HIV infection, heart disease, cancer risks, and psychiatric disorders. In addition, he also has experience in implementing his developed methods in software packages. His research has been supported by both NIH and NSF. He has collaborated on studies of prostate cancer, heart disease, psychiatric disorders, and environment risk assessment.

Gwen Collman

National Institute of Environmental Health Sciences

Gwen Collman, Ph.D., is director of the NIEHS Division of Extramural Research and Training where she leads approximately 60 professional staff in areas of scientific program administration, peer review, and the management and administration of about 1,500 active grants each year. She directs scientific activities across the field of environmental health sciences, including basic sciences (i.e., DNA repair, epigenetics, environmental genomics), organ-specific toxicology (i.e., reproductive, neurotoxicology, respiratory), public health-related programs (i.e., environmental epidemiology, environmental public health), and training and

career development. She also oversees the implementation of the Superfund Research Program (SRP) and the Worker Training Program (WTP).

Prior to her current role, Collman served in program development and management, beginning in 1992 as a member, then as chief of the Susceptibility and Population Health Branch. During this time, she directed research on the role of genetic and environmental factors on the development of human disease, from animal models of genetic susceptibility to population studies focusing on etiology and intervention. She was responsible for building the NIEHS grant portfolio in environmental and molecular epidemiology and developed several complex multidisciplinary research programs. These include the NIEHS Breast Cancer and the Environment Research Centers Program, the NIEHS/EPA Centers for Children's Environmental Health and Disease Prevention, and the Genes, Environment, and Health Initiative. Also, under her guidance, a team created a vision for the Partnerships for Environmental Public Health program for the next decade.

Brent Coull

Harvard T.H. Chan School of Public Health

Brent Coull, Ph.D., is a Professor of Biostatistics and Environmental Health, and Associate Chair of the Department of Biostatistics at the Harvard T.H. Chan School of Public Health. Coull has over 20 years of experience in a wide range of biostatistical applications to environmental health research, including the health effects of air pollution and children's environmental health. Coull currently co-directs the Environmental Statistics Program at the Harvard Chan School, is Principal Investigator of the Environmental Statistics and Bioinformatics Core of the Harvard NIEHS Center, and is the associate director of the Harvard-EPA Air and Energy (ACE) Research Center. Coull also directs an NIEHS-funded T32 training program in biostatistics for environmental health research.

Coull's primary research interests focus on integrative modeling of exposure data collected at multiple spatial and temporal scales, measurement error issues associated with the use of outputs from such models in risk assessments, statistical methods for identifying critical windows of exposure in children's health, and methods for analyzing the health effects of complex environmental mixtures in complex epidemiological study designs. Coull received his doctorate in Statistics from the University of Florida.

David Dunson

Duke University

David Brian Dunson, Ph.D., is an Arts and Sciences Distinguished Professor of Statistical Science and Mathematics at Duke University. His research focuses on developing statistical methods for complex and high-dimensional data. Particular themes of his work include the use of Bayesian hierarchical models, methods for learning latent structure in complex data, and the

development of computationally efficient algorithms for uncertainty quantification. He is currently serving as joint editor of the Journal of the Royal Statistical Society, Series B.

Dunson became a fellow of the American Statistical Association in 2007, the same year in which he won the Mortimer Spiegelman Award given annually to a young researcher in health statistics. He became a fellow of the Institute of Mathematical Statistics in 2010, and in the same year won the Committee of Presidents of Statistical Societies Presidents' Award. He was named Arts & Sciences Distinguished Professor in 2013. Dunson earned a bachelor's degree in mathematics from Pennsylvania State University in 1994 and completed his doctorate in biostatistics in 1997 from Emory University.

Katherine Ensor

Rice University

Katherine Ensor, Ph.D., is the Noah G. Harding Professor of Statistics in the George R. Brown School of Engineering at Rice University where she serves as director of the Center for Computational Finance and Economic Systems (CoFES). Ensor is overseeing the development of the Kinder Institute Urban Data Platform, a resource for the greater Houston area. She served as chair of the department of statistics from 1999 through 2013. Ensor, an expert in many areas of modern statistics, develops innovative statistical techniques to answer important questions in science, engineering and business with focus on the environment, energy, and finance. She is a fellow of the American Statistical Association, the American Association for the Advancement of Science and has been recognized for her leadership, scholarship, and mentoring. She served as vice president of the American Statistical Association from 2016 through 2018 and is a member of the National Academies Committee on Applied and Theoretical Statistics. Ensor is a member of the governing board for the NSF Institute for Pure and Applied Mathematics. She holds a Bachelor of Science in Education and Master of Science in mathematics from Arkansas State University and a Ph.D. in Statistics from Texas A&M University.

Chris Gennings

Icahn School of Medicine at Mt. Sinai

Chris Gennings, Ph.D., is director of the division of biostatistics and research professor in the department of environmental medicine and public health at the Icahn School of Medicine at Mount Sinai. She is the director for the Statistical Services and Methods Development Resource for the Children's Health Exposure Analysis Resource (CHEAR) Data Center and the Director of the Biostatistics and Bioinformatics Core of the Mount Sinai P30 Transdisciplinary Center on Early Environmental Exposures. Prior to joining Mount Sinai in 2014, Gennings held positions at Virginia Commonwealth University, including as professor in the department of biostatistics and director for the Clinical and Translational Research Incubator. She received a doctorate in biostatistics from the Medical College of Virginia and a Bachelor of Arts in mathematics from the University of Richmond.

Gennings has been actively engaged in the field of mixtures for more than 30 years, focusing on design and analysis methodologies for studies of chemical mixtures. This has included methods for both toxicology and epidemiology/clinical studies. Recent work includes development of a nutrition index; development of weighted quantile sum (WQS) regression – a method that is robust to confounding concerns based on complex correlations among exposure to environmental mixtures; the development of tests for sufficient similarity, a novel approach that complements current cumulative risk assessment methods and does not require the default assumption of additivity; and development of the acceptable concentration range (ACR) model that provides empirical estimates of mixture regulatory guideline values using human observational data.

Bonnie Joubert

National Institute of Environmental Health Sciences

Bonnie Joubert, Ph.D., is a scientific program director in the Population Health Branch at the NIEHS and manages part of the extramural epidemiology program. Her portfolio includes molecular epidemiology; cardiovascular, respiratory, metabolic, immune, and kidney epidemiology research; as well as statistical methods development. She also co-leads NIEHS engagement in the H3Africa consortium. Bonnie received her Master of Public Health in epidemiology from Tulane University School of Public Health and Tropical Medicine, and her doctorate in epidemiology from the University of North Carolina at Chapel Hill. She has public health and research experience in Africa and computer programming proficiency for the analysis of big data. She spent time as a postdoctoral environmental health scientist at the EPA and a research fellow at the NIEHS in the Division of Intramural Research. Her prior research included genetic epidemiology of mother-to-child transmission of HIV, genome-wide association studies of respiratory disease, and epigenome-wide association studies of early life environmental exposures.

Marianthi-Anna Kioumourtzoglou

Columbia University

Marianthi-Anna Kioumourtzoglou, Ph.D., is an environmental engineer and air pollution epidemiologist. She holds a Master of Science in Public Health from the UNC Gillings School of Public Health, department of environmental sciences and engineering and a Doctor of Science in environmental health from the Harvard TH Chan School of Public Health, where she also conducted her post-doctoral fellowship. She is currently an assistant professor at the department of environmental health sciences at Columbia University's Mailman School of Public Health. Her research focuses on applied statistical issues related to environmental epidemiology, including quantifying and correcting for exposure measurement error, exposure prediction uncertainty propagation, and assessment of high-dimensional and complex exposures in health analyses. Her studies mainly—albeit not exclusively—focus on air pollution exposures and, additionally, on identifying vulnerable subpopulations and characterizing how risks may vary across neighborhood-level and other urban characteristics, as well as in a changing climate.

Marie Lynn Miranda
Rice University

Marie Lynn Miranda, Ph.D., is the Howard R. Hughes Provost and Professor of Statistics at Rice University in Houston, Texas, and an adjunct professor of pediatrics at Duke University and Baylor College of Medicine.

Miranda specializes in research on environmental health, especially how the environment shapes health and well-being among children. She is the founding director of the Children's Environmental Health Initiative, a research, education, and outreach program committed to fostering environments where all people can prosper. Miranda's formal educational background is rooted in mathematical, statistical, and economic modeling; her professional experiences integrate environmental health sciences with sound social policies. She is a leader in the rapidly evolving field of geospatial health informatics and has applied spatial analytic approaches to a wide range of scientific issues.

Miranda maintains an active research portfolio, with a funding history that includes the EPA, the NIH, the Centers for Disease Control and Prevention, the National Association of Chronic Disease Directors, the U.S. Department of Agriculture, the state of North Carolina, the Robert Wood Johnson Foundation, the Wallace Genetics Foundation, the Mary Duke Biddle Foundation, and The Duke Endowment. She maintains a deep and abiding interest in environmental and social justice. Her research group received the 2008 EPA Environmental Justice Award.

Miranda is a Phi Beta Kappa, summa cum laude graduate of Duke University, where she earned her bachelor's degree in mathematics and economics and was named a Truman Scholar. She has a doctorate and a Master of Arts, both in economics, from Harvard University, where she held a National Science Foundation Graduate Research Fellowship. She served on the faculty at Duke from 1990-2011, and then as dean of the School of Natural Resources and Environment at the University of Michigan for four years. Miranda became provost at Rice University in July 2015.

Marie Ellen Turyk
The University of Illinois at Chicago

Mary Turyk, Ph.D., is an associate professor of epidemiology in the division of epidemiology and biostatistics at the University of Illinois at Chicago School of Public Health. Her research focuses on the impacts of persistent organic pollutants (POPs), such as polychlorinated biphenyls, on hormone homeostasis and cardiometabolic diseases. In 2008, her work on hormone disruption by an emerging contaminant of concern, the flame retardant polybrominated diphenyl ethers, was the first major study published on this topic. Subsequently she led one of the first prospective investigations on the role of POP exposures in the development of diabetes, finding elevated diabetes risk in persons with greater exposure to a metabolite of the pesticide DDT.

Current collaborative projects focus on the impact of POPs on early and late transitions to diabetes, potential biological pathways and efforts to develop statistical methodology to examine the role of chemical mixtures on cardiometabolic outcomes. Turyk's interests also include translational projects, such as Promoting Healthy Seafood Choices in Asian Communities, which examines the balance of benefits and risks of seafood consumption in Chicago Asian communities and evaluates the efficacy of public health text messages in decreasing exposure to contaminants while maintaining consumption of healthy nutrients from fish. Turyk has also conducted research examining the impact of deteriorating housing conditions and allergens on asthma morbidity in Chicago communities and the effectiveness of home-based, multifaceted interventions in reducing asthma morbidity.

Thomas Webster
Boston University

Thomas F. Webster, D.Sc., is professor of environmental health at Boston University School of Public Health (BUSPH). He has a bachelor's degree from MIT and doctorate from BUSPH. Webster has been interested in the biological effects of mixtures since he was a graduate student when he was told both 1) that mixtures are too hard and 2) don't bother, it is just interaction and we know how to do that. He is currently working on mixtures from an interdisciplinary point of view: epidemiology, statistics, toxicology and exposure science. In addition to being PI of a PRIME grant, he is PI of an R01 on mixtures toxicology where his group is testing mathematical models of mixture effects in the laboratory with a particular focus on receptor-based mechanisms and pharmacodynamics. Webster also does research on exposure and epidemiology of compounds found in consumer products and water, e.g., PFAS, flame retardants, organophosphate esters and phthalates/phthalate alternatives.



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The background is a dark blue gradient. It features a perspective view of a grid of dots, where each dot is either red or blue. The dots are arranged in a way that creates a sense of depth, receding towards the top of the frame. Overlaid on this is a faint, semi-transparent pattern of binary code (0s and 1s) in a light blue color.

**Powering Research Through Innovative Methods for
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